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1 author:

Edward J. Calabrese
University of Massachusetts Amherst
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HISTORICAL BLUNDERS: HOW TOXICOLOGY GOT THE DOSE-RESPONSE RELATIONSHIP HALF RIGHT

E.J. CALABRESE

Environmental Health Sciences Program, School of Public Health, University of Massachusetts, Amherst 01003, USA
Fax: +1 413 545 4692; E-mail: edwardc@schoolph.umass.edu

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Abstract - Substantial evidence indicates that reliable examples of hormetic dose responses in the toxicological literature are common and generalizable across biological model, endpoint measured and chemical class. Further evaluation revealed that the hormetic dose response model is more common than the threshold dose response model in objective, head-to-head comparisons. Nonetheless, the field of toxicology made a profound error by rejecting the use of the hormetic dose response model in its teaching, research, risk assessment and regulatory activities over nearly the past century. This paper argues that the hormetic dose response model (formerly called the Arndt-Schulz Law) was rejected principally because of its close historical association with the medical practice of homeopathy as a result of the prolonged and bitter feud between traditional medicine and homeopathy. Opponents of the concept of hormesis, making use of strong appeals to authority, were successful in their misrepresentation of the scientific foundations of hormesis and in their unfair association of it with segments of the homeopathic movement with extreme and discreditable views. These misrepresentations became established and integrated within the pharmacology and toxicology communities as a result of their origins in and continuities with traditional medicine and subsequently profoundly impacted a broad range of governmental risk assessment activities further consolidating the rejection of hormesis. This error of judgment was reinforced by toxicological hazard assessment methods using only high and few doses that were unable to assess hormetic responses, statistical modeling processes that were constrained to deny the possibility of hormetic dose response relationships and by the modest nature of the hormetic stimulatory response itself, which required more rigorous study designs to evaluate possible hormetic responses.

Key words: Hormesis, threshold, linearity, dose-response, u-shaped, j-shaped, risk assessment, censorship, Arndt-Schulz Law, probit analysis, homeopathy, Hahnemann

INTRODUCTION

Hormesis is a dose-response phenomenon characterized by a low dose stimulation and a high dose inhibition. Depending on the endpoint measured, the hormetic dose response may be seen as an inverted U-shape as in the case of growth, longevity, or cognitive function or as a J-shaped curve as in the case of disease incidence (26) (Fig. 1).

The dose-response relationship is the central pillar of the pharmacological and toxicological sciences. Knowledge of the dose-response is critical for setting environmental, occupational and consumer health standards as well as administration and consumption of pharmaceutical agents. The historical foundations of pharmacology and toxicology are built upon the theoretical and practical beliefs of what the nature of the dose response relationship is for chemical and physical agents. Within this context, knowledge of the dose-response was derived from the research of numerous experimentally oriented scientists during the late 19th and early 20th centuries (68,69,70,74). In general, these research efforts revealed that the nature of the dose response was sigmoidal (i.e. S-shaped) with a marked increase in response between approximately 20-80%, while asymptotically approaching 0 or 100% at the tails of the distribution. This made estimation of the 50% value quite reliable, while estimations of <1 or >99% responses were highly uncertain (81). For a substantial portion of the 20th century, this served the practical purposes of researchers designing studies and for regulatory agencies estimating acceptable exposures of workers and the general public to toxic substances and patients to drugs.

The sigmoidal dose-response led to the belief that thresholds exist at low doses. Numerous observations suggested that as the dose was progressively decreased the response became more like the control value, regressing into the "noise" zone of the control and becoming

indistinguishable from it. Thus the belief in the threshold model was born, that is, a belief based on experience and data. So strong was this belief in the threshold dose response model as a fundamental component of general biological processes that it has subsequently ruled the fields of pharmacology and toxicology.

The only serious institutional challenge to the threshold dose response model throughout the 20th century dealt with the nature of the dose-response for carcinogens. In this case, concern over health consequences of exposures to radiation lead to the adoption of a linear at low dose assumption, thereby replacing the threshold model. This change was driven by the research of Muller (58) that X-rays could cause somatic mutations in a linear fashion and concern over cancer risks of the atomic bomb survivors. This public health protectionist perspective was extended to the world of chemical risk assessment for carcinogens where linearity at low dose has been the guiding toxicological philosophy of powerful governmental regulatory agencies in numerous countries.

Even though the threshold and linear at low dose models for non-carcinogens and carcinogens, respectively, have dominated the fields of pharmacology and toxicology, the hormesis dose response model has begun to offer a significant challenge to these models with claims of being more fundamental than either based on its greater frequency in the peer-reviewed literature, and capacity for generalization without restriction to biological model, endpoint measured, and chemical or physical agent studied (20,22,25). Despite these claims and supportive evidence,

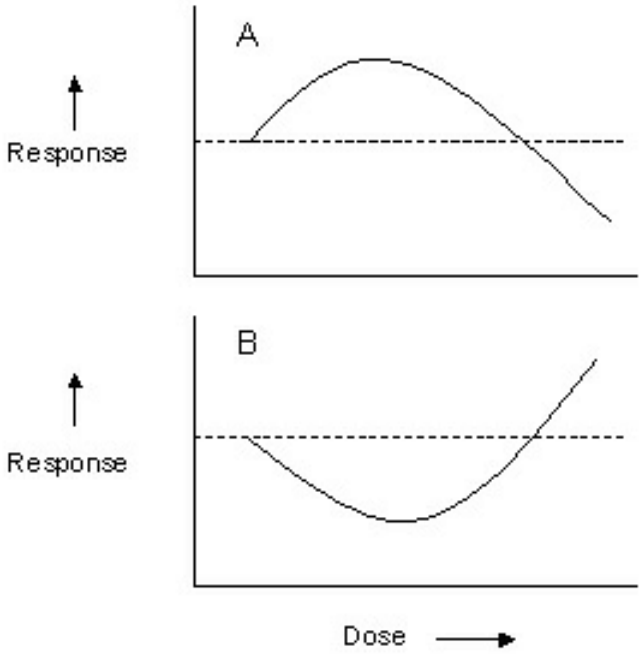

Fig. 1 Schematic representation of the hormetic dose response as represented by and inverted U- and a J-shape depending on the endpoint measured

the hormetic model has been, at best, laboring in obscurity and not taken seriously, while frequently being the object of ridicule. Although these perspectives and judgments are changing, it is important to consider why a **HORMETIC** dose-response model, arguably the most fundamental in the biological/toxicological sciences, fell into disrepute and stayed there for a century. The specific reasons leading to the failure of the hormetic dose response to be competitive in the 20th century will now be addressed.

HISTORICAL ANTIPATHIES: THE BATTLE BETWEEN "TRADITIONAL" MEDICINE AND HOMEOPATHY

The most important factor that contributed to the demise of the hormetic dose response model in the 20th century was its early and close association, one could say intimate, with the controversial medical practice of homeopathy. The key scientific discovery that lead to the modern understanding of hormesis was published by Hugo Schulz in 1888, reporting that low concentrations of various disinfectants enhanced the metabolism of yeasts, while being inhibitory at higher concentrations (71). For Schulz, these findings were very significant providing the explanatory principle of homeopathy. In previous research with a clinically "successful" homeopathic gastroenteritis treatment, Schulz found that the medicinal agent was unable to kill the microbe when applied in culture conditions. He opined that homeopathic remedies may act via enhancing the adaptive capacity of patients to fight off infections rather than via a direct killing action (38). Schulz was, of course, unaware that chemical agents may require bio-activation within the body which could kill the microbe (a possibility that would be tested today before drawing the immediate conclusion that he did).

Schulz's homeopathically supportive interpretation became widely known and he became a "cause celebre" in the homeopathic community that had been fighting a prolonged and bitter fight for both financial survival and scientific respect with the field of traditional medicine. The work of Schulz quickly became associated with homeopathy and, in fact, has been prominently cited even to the present time (6,7) as providing its underlying scientific principle.

This intertwined association of the hormesis concept with homeopathy proved to be a major strategic impediment for its acceptance in medically related disciplines such as pharmacology and toxicology. Intellectual leaders in these fields devoted considerable effort to emasculate the hormesis concept (i.e. called the Arndt-Schulz Law throughout much of the 20th century). Of particular note was the criticism of Alfred J. Clark, an eminent pharmacologist especially in the area of receptor biology, who published several books including *Applied*

Pharmacology (32) which by 1941 had seven editions and was translated into Spanish and Chinese, the *Mode of Action of Drugs on Cells* (33) and *Handbook of Experimental Pharmacology* (34), which had a deep and prolonged influence on the field. In fact, in the forward to the book, '*Towards Understanding Receptors*', Robinson (66) referred to the 1937 text as the "now classic monograph on General Pharmacology, a book that had great influence on a number of individuals".

Clark's criticism was devastating and repeatedly carried over to new editions of his 1933 and 1937 text books that were readily available to several generations of pharmacologists and toxicologists. He ridiculed homeopathy and its founder, Samuel Hahnemann, associated Hugo Schulz with homeopathy, attempted to trivialize the Arndt-Schulz Law, by suggesting that it is most likely explained by experimental error, and, even if true in limited situations, had no general application or meaning (Tables 1-3). To further denigrate the Arndt-Schulz Law, he linked it to the discredited concept of Vitalism, which had been highly controversial in the 19th century and early decades of the 20th century. Given the stature of Clark and the prominence of his books, there was little hope that the Arndt-Schulz Law and the concept of hormesis would find acceptance within the framework of traditional medicine.

The successful attempt of Clark to associate the Arndt-Schulz Law with homeopathy has been a recurring theme over the remainder of the 20th century, being strongly reinforced (Table 4) in a notable book on hormesis by biochemist Thomas Luckey (56). The continuous and prominent association of hormesis with homeopathy served to further diminish the likelihood of acceptance of the hormesis concept within the biomedical community.

Biostatistical modeling assumptions deny possibility of hormesis

In the mid 1930s serious attempts began to emerge to bio-mathematically model dose response data including the independent development of probit analysis by Bliss (8,9) and Gaddum (44). According to Salsburg (67), this represented a genuine advance since there was no guidance in the earlier publications of Fisher, "Student" or other early quantitative thinkers on how to proceed. Probit analysis has been broadly applied to toxicology and in fact the "insights gained from probit analysis form the foundation of much of the science of toxicology" (67). Probit analysis was used to directly estimate the threshold dose, making use of the maximum likelihood estimate (see the appendix of Bliss (9) in which the noted biostatistian RA Fisher utilized the maximum likelihood estimate to calculate threshold doses). This development was of far reaching significance since it required response values to be greater than the control, a constraint soon applied to the modeling of

Table 1 Quote relating to homeopathy and Hahnemann. Source: Alfred Clark- *The Historical Aspect of Quakery*. *Br. Med. J.* **2**: 589-590, 1927

Refers to Homeopathy as "absurd"
"The career of Hahmemann, however, is a striking example of the way in which a rebel against authority who commences with an appeal to reason may finish by establishing a dogmatic faith even more absurd than the orthodox traditions he tried to explode".

Table 2 Quotes relating to homeopathy and the Arndt-Schulz Law. Source: Alfred Clark - *The Mode of Action of Drugs on Cells*, 1933

High dilution scheme of Hahnemann Lacking Credibility - page 24
"Hahnemann, for example, claimed that drugs at the 30th potency produced reliable effects, and actions produced by similar dilutions are still occasionally described (e.g. Konig, 1927). A homeopathic potency means a dilution one hundredfold, and hence the 30th potency corresponds to a concentration of 1 part in 10^{60}. This works out at about one molecule in a sphere with a circumference equal to the orbit of Venus. Such results may be either believed or disbelieved, but their acceptance involves discarding the fundamental laws of chemistry and physics".
"Other results have been published which are almost equally improbable"
Associates Schulz with Homeopathy - page 195
"In 1885 Rudolf Arndt put forward the suggestion that if a weak stimulus excites an organism, then any drug in sufficiently weak dose ought to do this also. This suggestion was developed by Schulz, who had leanings to homeopathy".
Challenges the Biological Significance of the Arndt-Schulz Law - pages 195-196
"….many pharmacologists have pointed out that it (Arndt-Schulz Law) expresses no general truth. It is interesting to note that no trace of evidence in support of such a law can be found in the majority of drugs".
Hormesis probably confused with experimental errors - page 196
"As in the case of potential actions, evidence in favor of this law can easily be obtained from experimental errors".

Table 3 More quotes on homeopathy and the Arndt-Schulz Law. Source: Alfred Clark - *Handbook of Pharmacology*, 1937

Challenges Mechanistic Understanding of Hormetic Effects **-** page 215
"……laws have been enunciated which merely state that certain phenomena frequently occur, without providing any explanation for their occurrence. The Arndt-Schulz Law…..(is) (an) example of this type…".

Arndt-Schulz Law is Usually Discredited When Carefully Assessed **-** page 204
"Arndt-Schulz Law. This law states that any drug which causes stimulation at low concentrations will cause inhibition at high concentrations. This law is in accordance with homeopathic doctrines and hence has maintained a certain popularity. The law is true in so far that nearly all drugs if given in sufficiently high dosage or concentration will produce injury or death in living cells".
"The chief objection to the law is that it is obviously untrue in the case of most drugs that have been studied carefully".
"Many of the effects which appear to support this law have found simple explanations……".

Arndt-Schulz Law Was Related To Vitalism – page 36/example 1
"Diphasic actions of drugs on tissues are frequently observed, and their occurrence led to the postulation of the Arndt-Schulz Law, which states that drugs which paralyze at high concentrations stimulate at low concentrations. It is true that such effects are often observed but there is no necessity to postulate any mysterious (emphasis added) property of living tissues because similar effects are frequently observed with enzyme systems".

More Quotes on Homeopathy and the Arndt-Schulz Law

Arndt-Schulz Law Was Related to Vitalism - page 30/example 2
"This peculiar effect is mentioned here because it is the simplest example known to the writer of a reaction following the "Arndt-Schulz Law". In this case a high concentration of oxygen prevents the formation of HbCO but if hemoglobin is exposed to a low concentration of carbon monoxide, then a low concentration of oxygen may increase the formation of HbCO. Hence oxygen may be said to stimulate in low concentrations and to inhibit in high concentrations. This diphasic action can be explained on physico-chemical grounds and although our present knowledge is inadequate to explain most of the diphasic actions met with in more complex systems, yet there seems no reason to consider them as peculiarly mysterious (emphasis added)".

Challenges High Dilution Proposal of Hahnemann and Homeopathy - page 26
"….. Hahnemann claimed that drugs produced effects when given in the 30^{th} potency…… in the case of a drug with a molecular weight of 100, (this) corresponds to 1 molecule in about 100,000 liters. It is obvious that (when) a sample of a few c.c. of such a mixture is taken, the odds against the presence in the sample of a single molecule of the drug are at least a million to one. Hence the claims of the homeopathist conflict more immediately with the laws of mathematics, physics and chemistry than with the biological sciences. It does not appear necessary for pharmacologists to discuss the evidence adduced by the homeopathists until the latter have succeeded in convincing the physicists that they have demonstrated the existence of a new form of subdivision of matter. It may be mentioned that the existence of such recognized subdivisions of the atom as electrons etc. does not help the homeopathic claims in a significant manner because, to explain the results of Hahnemann, it is necessary to assume that a molecule can be divided into millions of sub-units".

Table 4 Hormesis and homeopathy. Source: *Ionizing Radiation and Hormesis*, Luckey, T., 1980

Hormesis as the Scientific Basis of Homeopathy – page 58
"The experimental data suggest that hormesis provides a scientific basis for homeopathy and some kinds of acupunture".

Hormesis, High Dilution and Homeopathy - page 60
"Early doctrines of medicines were based upon the application of small or minute doses to cure a variety of diseases. Data from hormesis provide experimental support for such concepts. The similia curantur doctrine of Hippocrates suggested the application of drugs that gave reactions similar to disease symptoms (6). This was followed by the signature doctrine: disease may be treated by material that physically resemble the affected organ; e.g. **disease may be treated by material that physically resemble the affected organ; e.g**. eat a Cyclamen leaf to cure an earache (448). The Hippocratic doctrine was modified by Hahnemann (450a). Homeopathic medicine is still practiced in many countries. It has been severely criticized on the basis that unreal dilutions have been used; however, this does not take into account adsorption phenomena during triturations, the use of real dilutions of most prescriptions, and an appreciation that the art of medicine is more than the administration of molecules. A major difference between homeopathy and hormesis is that the former adhere to special drugs for each syndrome, while the latter suggests many agents could accomplish the same results. Homeopathy relies on exceptional results in human testing. Hormesis encompasses both Hippocrates' first doctrine as well as his second, contraria contrais curantur; ills are cured by antagonistic materials. The specific drugs of modern medicine are in another category; they can act in specific ways. The popularity of a handful of antibiotics for dietary promotants suggests a specificity exists in hormesis; this may be due to market characteristics, such as cost, stability, toxicity, taste, patents, or to the limited knowledge of the trade".

carcinogenic dose responses (18), even when responses in the low dose zone were below control values. In essence, responses below control values were considered noise or variability, not a real effect. The decision to constrain responses in the low dose range to be asymptotically above the control value had the net effect of denying the potential reality of the hormetic dose response. This type of bio-mathematical modeling constraint became incorporated into cancer risk assessment procedures and is employed today by regulatory agencies such as the U.S. EPA and FDA that assume the cancer dose response relationship is linear at low dose.

IMPACT OF MEDICINE ON TOXICOLOGY AND BEING "TOXICOLOGICALLY CORRECT"

As noted above, the long-standing confrontation between traditional medicine and homeopathy was an important factor affecting the rejection of the hormesis concept by the medical and biomedical communities. In the case of toxicology, its lineage directly traced to the field of pharmacology. Many of the early leaders in the field of toxicology were trained in pharmacology departments within medical schools. In fact, the first journal of the U.S. Society of Toxicology was entitled *Toxicology and Applied Pharmacology*, clearly showing its historical ties. Many of the early leading toxicologists in the U.S. can trace their academic genealogy back to one of several originators of pharmacology in the U.S., such as John Jacob Abel at Johns Hopkins University, Arthur R. Cushney at the University of Michigan, and other such founding fathers who were trained in various European centers. The impact of medicine on the field of toxicology remains a dominant one with leading centers of toxicological research residing within medical schools. Even the institutionizing of board certification of toxicologists since the early 1980s is another manifestation of the dominating influence of medicine on the directions of toxicological thought. It is the contention here that its historical origins within the traditional medicine establishment have had a strong impact on how and why toxicology as a discipline rejected hormesis, finding strong support for such a rejection in the influential texts of leaders like Clark.

A major question in assessing the rejection of the hormesis concept by the pharmacological/toxicological communities relates to the issue of who most strongly influences the "scientific environment"; this affects what people may say, hear, write, read or see and may take many forms starting with decisions concerning who serves on influential panels, committees and editorial boards, to what gets studied, as well as who receives funding and gets promoted. Such decisions in our open society are conducted typically under the banner of a quality control system called peer-review, the premise of which is that all ideas and people get a fair hearing, and in general, over time, the best ideas and most insightfully productive people advance, while the lesser endowed ideas and performing scientists are not as successful.

The present paper argues that the normal process of "peer-review" with respect to the hormesis concept became "institutionally" affected by a type of historical "toxicological correctness" that was an outgrowth of the prolonged antipathies between traditional medicine and homeopathy. Moreover, this failure was far greater than occasional irregularities in the common peer review process, but a more insidious phenomenon occurring at multiple levels (e.g. academic, governmental, professional society, journal activities), effecting the most central aspect of toxicology (i.e. the nature of the dose response) over several generations of pharmacologists/toxicologists. What makes the situation even more challenging and difficult to recognize is that this censoring-like behavior eventually became thoroughly and subtly integrated into the entire texture of the field such that it does not even require an apparent conscious effort for its multi-faceted efficient continuation. That is, it simply became a routinized way of thinking, deciding and acting after nearly a century. The intellectual rejection of the hormesis concept became nearly complete when it was continually re-enforced by its absence in each new edition of textbook, lack of inclusion in each subsequent annual professional society meeting, and non-priority within governmental funding of regulatory programs relating to toxicology and risk assessment.

INFLUENTIAL OPPONENTS

The battle against the acceptance of the Arndt-Schulz Law was led by some of the most stellar biomedical scientists of the day. As noted above, the clear intellectual leader was Alfred J. Clark, a pharmacological researcher of great distinction, an academic leader at one of the most prestigious institutions (University of Edinburgh, UK), and a highly respected advisor to various governmental agencies. Besides awards and recognition, he was well connected with other leaders in the field of medicine and pharmacology. For example, Clark was one of the 30 "charter" members of the British Pharmacological Society in 1931 (62). This founding group of pharmacologists was extremely prestigious with eight (i.e. H.H. Dale; W.E. Dixon; J.H. Burn; K.J. Franklin; A.J. Clark; J.H. Gaddum; A. St. Huggett; E. Mellanby, and E.B. Verney) becoming members of The Royal Society (British equivalent of the US National Academy of Sciences) (79), three (Dale, Mellanby and Verney) were nominated for the Nobel Prize in Biology and Medicine, with one (Dale) receiving it in 1936. In addition, Dale (1924) and Mellanby (1936) were

winners of the prestigious Royal Archive award for their research achievements. Most of the members became academic leaders in pharmacology (e.g. W.J. Dilling – University of Liverpool, UK; P. Hamill - Cambridge University, UK; Huggett – University of London, UK; E.B. Verney – University of Edinburgh, UK), as well as major textbook authors (e.g. R. Stockman; W.A.M. Smart; K.J. Franklin; J.R. Gaddum), while A.St. Huggett was honored by *Lancet* for having the second most cited paper in the history of the journal up to 1983 (*Lancet*, 1984) (2). Clark also had close professional relationships with those, such as John W. Trevan, J.R.. Gaddum, R.A. Fisher and C.I. Bliss, who were transforming pharmacology into a quantitative science. Clark was commonly noted for providing assistance to such leading researchers, including the acknowledgement by Bliss (9) relating to the creation of probit analysis and the constraining of all treatment group responses to exceed the control value.

Clark also represented the British Pharmacological Society on the Editorial Board of the *American Journal of Pharmacology* and *Experimental Therapeutics* (1935-1939), and was on the editorial board of the *Quarterly Journal of Experimental Physiology* from 1935 until his death in 1941. He also served on the Medical Research Council for several terms; this was considered an recognition of how highly his judgments were regarded. He also was a member of the Pharmacology Subcommittee of the British Pharmacopoeia from 1928 until his death (82). In his Inaugural Address as the Professor of Materia Medica and Pharmacology at the University of Edinburgh replacing the deceased Clark, J.H. Gaddum (45) stated that Clark "was a great man and a very lovable man. He became the leading pharmacologist in these islands...".

The British pharmacological community was a very close and influential one. Its members were central to the development of pharmacology and toxicology. With so many of its group being unusually gifted, productive and academic leaders, it was a substantial compliment by Gaddum, himself the recipient of an acknowledgment in the Nobel lecture of Dale (39), that Clark "became the leading pharmacologist in these islands". Given the noted achievements and high personal regard with which Clark was held by his colleagues, it follows that his strong, repeated and uncompromisingly sharp criticisms of Hahnemann, homeopathy, and the Arndt-Schulz Law had the capacity to cast a broad, influential and intimidating shadow over the medical, pharmacological and biomedical communities for many years. In fact, Clark's highly influential *Handbook of Experimental Pharmacology*, which was very critical of the Arndt-Schulz Law, was published through seven editions, into the 1970s, more than 30 years after his untimely death at age 54 following surgery due to intestinal blockage (35,43). This authoritative public criticism by one of Clark's stature, likely became a form of professional intimidation that infiltrated the field, affecting its collective thinking, attitudes and behavior. Such intimidation is especially effective when it affects the reputation of distinguished scientists, establishing a type of "discipline" on the field, as with August Bier, who was repeatedly nominated for the Nobel Prize for his work on spinal cord anesthesia. Once he began to study possible scientific foundations of homeopathy, Bier's stature in the field became markedly diminished (46).

One of the criticisms of homeopathy (and by association hormesis) that Clark forcefully made is that homeopathic remedies have no molecules in the preparation after numerous dilutions; yet their adherents insist that such treatments have real effects. While this is a legitimate criticism of the high dilutionist wing of the homeopathic field of which Hahnemann was the leading historical figure, Clark never mentioned or even implied that homeopathy was far from monolithic on this point. In fact, some 70 years before the publication of his *Handbook of Experimental Pharmacology* (34), the vast majority of homeopathic practitioners were adherents of the low dilutionist school (i.e. molecules in concentrations where quantifiable measurements could be made), a significant characterization never mentioned by Clark. Even though substantial literature existed on hormetic dose responses in the 30-40 years prior to publication of his critical books (27-31), he either choose to ignore numerous reliable examples of hormetic findings in various biological systems or simply did not adequately research the area. Instead, he selected examples of biphasic dose responses that were easily trivialized.

Clark also attempted to associate homeopathy with vitalism (Table 3), a discredited holdover idea of the 19th century. There was a basis for legitimate criticism, but only insofar as it was directed to the high dilutionist-wing of homeopathy. As stated by Coulter (37), "the 'highs' maintained that the highly diluted remedy contains an 'animus', the inmost power of any drug (which) is an efficient, immaterial, although substantial principle, in other words, an essence of power of which the visible drug constitutes the body, the material substratum… and that the process of dilution, trituration, and succussion enhances this medicinal force. To the argument that science can find no basis for the supposed power of the high dilutions, the 'highs' replied that science is not yet perfect and that future research would vindicate their position. For the time being, they held, the clinical evidence was too overwhelming to be denied".

"The 'lows,' however, did deny the theory of dynamization as 'a fanciful creation of Hahnemann….a form of medical spiritualism which is unsound in theory and very prejudicial in the interests of true homeopathy…. recognition and advocacy of the false theory of dynamization must cease – it is the embodiment of error".

There were many weaknesses in the arguments of Clark from the homeopathic and scientific perspectives. The most likely possibility of a refutation would have been from Schulz, but he had died in 1932; other notable supporters of the Arndt-Schulz Law such as August Bier in Germany, who had nominated Schulz for the Nobel Prize in Biology and Medicine in 1931 or American researchers such as Winslow, Branham, and others never came forward. The net result was that the hormesis concept was unfairly linked with high dilutionist homeopathic principles leading to its denegration and ridicule even to the present time (57).

As one reflects on the career of Clark, it is surprising that he would have made such a limited and highly selective review of the scientific literature in this assessment of the biological foundations of the Arndt-Schulz Law before drawing such definitive, opposing and strident conclusions. Clark was a very detailed and objective scholar based on the several singly authored texts. In the case of the Arndt-Schulz Law, it would appear that he approached the problem in a similar manner. However, a detailed assessment of the literature of that time period reveals just the opposite. The same is the case for the superficial way in which he evaluated the medical practice of homeopathy.

THE TIMING OF CRITICISM AND DOSE RESPONSE CONCEPT CONSOLIDATION

The "intellectual victory" over the concept of hormesis by the emerging toxicological community came at a time of concept consolidation within the academic and governmental communities over the nature of the dose response. The threshold theory of dose response was being adopted within the radiation health assessment community as well as by those developing chemical exposure standards for drinking water and industrial contaminants. More specifically, the radiation community had derived what was termed as a "tolerance dose", based on a threshold dose response concept, for acceptable levels of exposures for workers and patients. This was based on a fraction of the erythema dose, that is, the exposure needed to produce a discernable reddening of the skin (59). The tolerance dose was consistent with the concept of recovery from any sub-clinical effects. Various international groups, such as the International X-Ray and Radium Protection Committee (1928), the precursor of the International Commission of Radiological Protection (ICRP), and the U.S. Advisory Committee on X-Ray and Radium Protection (1929), the predecessor of the National Council on Radiation Protection and Measurements (NCRPM) (61), all employed the tolerance dose as the basis of their exposure standards from the mid 1920s to the mid 1940s [see Calabrese (21) for a review]. Thus, the radiologically-based tolerance dose, which was founded on the threshold dose response model, was therefore a well established concept that was fully integrated into international health decision making actions during the period of Clark's principal publications on the dose response.

During this general time framework, C.I. Bliss published a remarkable series of papers demonstrating how biostatistical modeling, with an emphasis on probit analysis, could be readily applied to a variety of biological disciplines including entomology, microbiology, food science, radiology, pharmacology and toxicology amongst others (8,10-14). These papers were a powerful confirmation of the threshold dose response in toxicology research and provided a universal scientific framework to evaluate the broad spectrum of dose responses, independent of biological model, endpoint measured and chemical or physical stressor. It also provided the means to not only to estimate practical thresholds but to design studies in an optimized way to assess statistical significance. Such concepts were consistent with, and soon led to, the suggestion of the concept of Safety Factors as early as the mid 1930s (42), and their refinement and institutionalization within the U.S. FDA almost two decades later.

This twenty year period was very significant because it was when the basic frameworks for hazard assessment and risk assessment developed. The concept of hormesis had been pushed far to the side and never was seriously discussed during this period of formalized dose response concept consolidation. The only serious challenge to the threshold model framework involved the assessment of carcinogens which subsequently led to the replacement of the threshold model with linear at low dose modeling. This change in thinking first became formalized in 1954 when the NCRP replaced the concept of tolerance dose with permissible dose, suggesting that there was no "safe" exposure to radiation. Within the next five years, this concept became solidified as the UN incorporated it into its radiation health framework, as did the U.S. Federal Radiation Council in 1959. This change in perspective would ultimately affect the regulation of chemical carcinogens as seen in the highly influential recommendations of the U.S. NAS Safe Drinking Water Committee (60) to the U.S. EPA. The concept of hormesis was intellectually beaten and functionally dormant with only occasional brief re-awakenings as seen in papers such as that by Smyth (75) entitled "Sufficient Challenge" that tried to resuscitate the Arndt-Schulz Law by then being incorporated into the terminology of hormesis.

MISUNDERSTANDING WHAT HORMESIS IS

The Arndt-Schulz Law, which was initially based on data with microbial toxins, was generally defined as: weak

irritants stimulate activity, medium irritants depress it, and strong irritants halt it. This rather unsophisticated early conceptual definition did not address the issue of time within the dose response evaluation. This lack of a temporal consideration was to be a major stumbling block to the understanding of hormesis and a basis for disagreements amongst supporters and opponents.

By the latter part of the 1890s, evidence emerged that low dose stimulation to chemical toxins may represent an overcompensation to a disruption in homeostasis, a concept first proposed by Townsend in 1899 (80) and later supported in convincing experiments by Branham (17) and others. This was an important advance not only conceptually but also for its potential to impact experimental protocols. Similar findings with radiation by Smith (73) demonstrated that stimulation of mycelium growth was a reproducible phenomenon except that it occurred only after the UV-induced damage with subsequent stimulation representing an overcompensation response.

The conclusion that the stimulation was not a direct one, but was only in response to damage, was considered by some as a direct refutation of the Arndt-Schulz Law. This refutation was adhered to by a number of highly prestigious radiation health scientists in the early decades of the 20th century, most notably by Holzknecht who had studied with Roentgen for three years, established the first method for measuring X-rays, created the International Society of University Professors of Medical Radiology and was the first European professor of medical roentgenology. His views were adopted by various international leaders such as Shields Warren, the prestigious Harvard professor and first Director of the Division of Biology and Medicine of the U.S. Atomic Energy Commission (See 30 for a review). Warren (83) noted that the *"assumption that small doses of X-ray or radium radiation are stimulatory (the Arndt-Schulz Law) is invalid. The slight evidences of proliferative activity offered as evidence by the proponents of this hypothesis are in fact only reparative responses to the injury that has been done"* (emphasis added). Recognition of reparative overcompensation following radiation-induced damage was commonly observed in reports as early as 1920 by Hektoen (48) head of Pathology at the University of Chicago with regard to antibody production, and by Pohle (63), Koga (54), Tenneff and Stoppani (78), and Schurer (72) for enhancement of reticuloendothelial activity. Confirmation of such findings was subsequently reported by Bloom and Jacobson (15), Dunlop (40) and Taliaferro and Taliaferro (77) and others. The rejection of the Arndt-Schulz Law by prestigious individuals in influential positions, such as Shields Warren, which was based on a conclusion that the stimulation was simply an example of a response to damage rather than a direct effect, was a critical scientific judgment that led to the marginalizing of the hormesis concept. Moreover, these leading opponents to the Arndt-Schulz Law neglected to suggest that the process being rejected was a basic feature of the toxicologic dose response curve observed in plant and animal models independent of whether the damage was caused by chemical toxins or radiation. Since the "stimulation" (i.e. overcompensation response) was indeed modest (i.e. only 30-60% greater than the control at maximum), consistently distanced from the traditional threshold (i.e. NOAEL value) with an overall range of about one order of magnitude, it supported the conclusion that this response was most likely compensatory to a limited induction of damage. However, instead of providing a refinement of the Arndt-Schulz Law to incorporate a temporal feature and to consider a modest overcompensation response which could account for the limited stimulation, the judgment was to reject the Arndt-Schulz Law and the hormesis concept. The most striking aspect of the historical unfolding of the hormesis story is that over 60 years later the definition of hormesis that is most consistently recognized and accepted incorporates an overcompensation response following a disruption in homeostasis (24), the very basis of its earlier rejection! While Warren and other scientific leaders, especially those in the radiation health area got the scientific concept right, they missed its biological and societal significance, thereby marginalizing its role to biological irrelevancy.

TOXICOLOGICAL LEGACY: HIGH / FEW DOSES

Perhaps the key feature in studying hormetic effects is having the proper study design. It would be ideal to have the capacity to assess the entire dose response continuum including responses above and below the traditional toxicological threshold. At a minimum, this suggests the use of 4-5 doses, plus a concurrent control and knowledge of temporal patterns of response. More specifically, the doses would include one that would define the lowest dose that would cause a significant response above the threshold (e.g. lowest observed adverse effect level; LOAEL), the threshold response (e.g. no observed adverse effect level – NOAEL), at least several (2-3) appropriately spaced doses below the threshold response level. In contrast to the above, toxicological assessments typically used two or three doses to define the LOAEL and the NOAEL with no consideration for assessing responses to doses below the NOAEL. Given this focus on defining the higher end of the dose response continuum and achieving it with a limited number of doses, there would be little opportunity to observe and assess hormetic effects. This would also be the case in rodent studies of short term duration (2-13 weeks), since control animals would not be expected to develop diseases in such a short period, making it unlikely to

observe hormetic responses in such hazard assessments.

The derivation of NOAELs and LOAELs became a focus for regulatory agencies since it was essential for deriving exposure standards for toxic substances in various environmental media. Consequently, large-scale funding programs involving academic research centers and private and public sector laboratories have been created to conduct hazard assessment research with the intention of deriving NOAELs and LOAELs for toxic agents of concern.

This lack of consideration of the possibility of an hormetic response is based, in part, on the belief that the most fundamental nature of the dose response is the threshold dose response model. Once this belief was accepted, it affected decisions concerning the study design and other research protocols that ultimately led to the creation of large toxicological databases, principally derived from high dose and few dose studies, and not surprisingly with little or no evidence of hormesis.

DISCUSSION

This paper argues that the field of toxicology made a profound error concerning the nature of the dose-response relationship by its historic rejection of the hormesis concept. How an entire field of study made an error of fundamental importance and continued to embrace the error over approximately a century is not only of academic interest to the fields of toxicology and intellectual history, but to society itself concerning how this mistake affected public policies for research funding, environmental regulation, drug development, clinical therapies and numerous other functions affected by the dose response relationship.

Although the cause of this error of toxicological judgment, as noted above, is complex and multi-faceted (Table 5), it may be reduced to a few broadly integrative themes. Most significant was the protracted and intense conflict between traditional medicine and homeopathy which created the enduring framework for error on either side of the debate, including Schulz's overinterpretation of his interesting and novel findings and pressing them into the immediate service of homeopathy. There was a strong counter-reaction by opponents of homeopathy to reject the scientific findings of Schulz, principally because it was proposed to provide the major biomedical foundation to support homeopathy. The proponents of traditional medicine's "political wing" then easily ridiculed the more extreme elements of homeopathy as seen within the high dilutionist element led by Hahnemann, and unfairly sought to link Schulz and his findings to the high dilutionist homeopathic movement. The leading elements of the "attack" on Schulz and his hypothesis were by the brightest, most accomplished, best positioned and connected scientists of the day as seen with A.J. Clark.

Given the expanding power of traditional medicine in the early decades of the 20th century and the historical demise of homeopathy world-wide, especially in the U.S. following the damning Flexner report of 1910 (41), there was little opposition to prevent the marginalizing of homeopathy and its "explanatory principle". This marginalizing was efficiently maintained since traditional medicine established a domineering intellectual suppression over the field when pharmacology and toxicology were emerging from it. Traditional medicine was able to extend its domain even further into the realm of governmental regulatory activities when the first several generations of toxicologists, who would, by and large, be products of traditional medical school training and often with MD degrees, assured the concept consolidation of the dose response process and affected the framework for risk assessment. This process directed the evolution of hazard assessment, risk assessment, testing requirements on drug and chemical companies, the activities of professional societies, direction and contents of biomedical journals, and what would be taught to future generations of toxicologists. This has proven to be an intellectual

Table 5 Factors contributing to the historical demise of hormesis

- Powerful conflicts with traditional medicine and homeopathy
- Toxicology directly emerges from traditional medicine
- Influential opponents to the hormesis concept controlling the vehicles of communication
- Influential opponents (radiation) accepting data that supports hormesis and denying that it is hormesis
- Biostatistical modeling being constrained to deny hormesis
- Rejection of hormesis occurring during the period of toxicological concept consolidation
- No intellectual counterforce at the time of concept consolidation (not yet addressed)
- Early supporters of the hormesis concept lack understanding of its dose-time response features
- Hormesis being difficult to prove experimentally without proper study designs
- Powerful regulatory agencies adopting rival dose response models;
- Governmental hazard assessment protocols making it highly unlikely to observe hormetic effects
- Being shunned from standard texts, society meetings and academic teaching
- Being excluded from research funding possibilities in major governmental grants programs
- Biological/societal implications not appreciated nor anticipated.

dominance that became a way of life for biomedically trained scientists that to all intents and purposes seemed rigorous, fair, and objective. Yet, as the present analysis has shown, it was only partially true. This "way of life" also had a significant element that was biased, inaccurate, dressed in an appeal to authority and professionally intimidating. It is within this historical mantra of the antipathies between traditional medicine and homeopathy that the winners (i.e. traditional medicine) neglected to heed the words of one of their own, that is, Ferdinand Hueppe, the author of an authoritative text on bacteriology (51), a protégé of the famous Robert Koch, and himself a nominee for the Nobel Prize, that Schulz's science was strongly supportable and should not be rejected despite his association with homeopathy. For it was in this historical blind spot, where the politics of two medical systems were embattled, that the winning side effectively censored the opponent's "explanatory principle", when it should have been embracing it as its own.

The effects of this century-long conflict have been as destructive as they have been overlooked, affecting the questions that toxicologists ask and assess, the biological models selected and often the endpoints measured, design of studies, the types of resources needed and employed in toxicological research, exposure standards for carcinogens and non-carcinogens, the cost of environmental and occupational health standards, approaches to risk communication for the general public, and a whole host of clinical opportunities to exploit for patient benefit, amongst others. As a result of getting the below NOAEL half of the dose response wrong, numerous opportunities have been missed and inappropriate strategies for addressing many societal issues have occurred which will need addressing and likely revisions.

Regardless of the scientifically depraved history of hormesis, it is important to note that the field of toxicology has begun to re-examine the underlying data that support the hormesis hypothesis. Within the past several years, the hormesis concept has been incorporated into the two leading toxicological textbooks (3,53) and highlighted at recent annual meetings of the Canadian and U.S. SOT. Further evidence of a toxicological awakening on the topic of hormesis is evidenced by the journal *Science* (52) providing substantial coverage and an invited Commentary in *Nature* (23). Likewise, hormesis has been the object of entire articles in *Discover* (49); *Scientific American* (65); *Environmental Science and Technology* (64); and *Chemical and Engineering News* (50); *Chemistry and Industry* (19); *European Molecular Biology Reports* (47) as well as numerous prestigious more popular publications [*Wall Street Journal* (4); *Boston Globe* (36); *Baltimore Sun*, (5); *U.S. News and World Report* (16); *Forbes* (55); *Fortune* (76); *London Times* (1), and others.

Despite the clear success that hormesis is beginning to experience within the toxicological community, the present paper raises an even more significant and foreboding issue than "simply" the incorrect rejection of the hormetic model as a legitimate and possibly fundamental dose response model within toxicology. For the question must be asked whether other such examples of intellectual censorship exist within society in general and science in particular, but in an undetected state. At least in the field of toxicology, we have finally detected ours (or at least one of them).

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